REMARKS

Claims 65-66, 70, 71, and 80-82 are pending in the application. New claims 84 and 85 have been added.

Claims 65-66 were rejected under 35 U.S.C. § 112, first paragraph. Claims 65-66 were also rejected under 35 U.S.C. § 102(b). Each of these issues is addressed as follows.

Claim Amendment

Claim 65 has been amended to include the feature that a monovalent antibody fragment "prevents the binding of von Willebrand factor (vWF) to human platelet GPIb." Support for this amendment may be found, for example, at page 6 (line 29) through page 7 (line 5), and page 10, lines 15 to 17, and page 26, lines 9 to 16 of the specification.

New claims 84 and 85 have been added. Each new claim is directed to subject matter deemed allowable in the advisory action mailed April 24, 2006.

No new matter has been added by this amendment.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 65-66 were rejected under 35 U.S.C. § 112, first paragraph for an asserted lack of enablement in Applicants' specification. In particular, the Office asserts that "[t]he specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation." As applied to amended claim 65, Applicants respectfully traverse this rejection.

With regard to the specification, the Office asserts:

> [The specification] does not reasonably provide **enablement** for a pharmaceutical composition comprising any monovalent antibody fragment with binds in vivo to human platelet glycoprotein GPIb without incurring thrombocytopenia in claim 65, wherein the fragment is a Fab fragment or a single variable domain. [Emphasis original.]

Applicants respectfully disagree.

Applicants note that the test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1318 (Fed. Cir. 1985). The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Applicants' specification meets this standard.

Claim 65, as amended, reads:

> A pharmaceutical composition comprising a monovalent antibody fragment which prevents the binding of von Willebrand factor (vWF) to human platelet glycoprotein Ib (GPIb) and binds *in vivo* to human platelet GPIb without incurring thrombocytopenia and a pharmaceutically acceptable carrier.

Applicants first note that the specification, for example, at page 6 (lines 29-32) and 14 (lines 15-20) describe monovalent antibody fragments and standard methods useful for producing such fragments. Moreover, the specification describes how one skilled in the art can test for the efficacy of a monovalent antibody fragment. For instance, Example 6 of Applicants' specification describes how to assess inhibition of vWF binding using standard methods known in the art at the time the application was filed. Example 6 extensively illustrates how to perform ristocetin-and botrocetin-induced aggregation assays to study whether vWF interacts with GPIb. In this regard, Applicants again direct the Examiner's attention to the Declaration of Dr. Hans Deckmyn (copy enclosed) previously filed in this case. Dr. Deckmyn, using standard methods known at the time the application was filed, generated Fab fragment of RMP15 (Kulkarni et al., Journal Clinical Investigation 105:783-791, 2000). Dr. Deckmyn further provided data on the anti-GPIb alpha antibody RPM15. Dr. Deckmyn also noted that, even though RPM15 induces thrombocytopenia as IgG, the monovalent RMP15 Fab fragments do not induce thrombocytopenia *in vivo*.

In view of these teachings, Applicants' specification clearly enables how to make and use monovalent antibody fragments recited in the present claims. Absent documentary evidence showing that such antibody fragments could not be produced by a skilled artisan using routine techniques, Applicants submit that this basis for the rejection should be withdrawn.

Apart from the general concerns regarding the specification expressed above, the Office has also cited Asch et al. (J. Clin. Invest. 81:1600-1607, 1988) as support for the general unpredictability of the methods involved in producing a monovalent antibody fragment. Here the Office asserts:

> [Asch's] [ ] GPIb alpha specific 3G6 monoclonal antibody did not inhibit ristocetin-induced platelet aggregation (see page 1600, under antibodies in particular). A fragment of 3G6 monoclonal antibody including Fab and a single variable domain would be expected to inhibit ristocetin-induced platelet aggregation and hence un-functional monovalent antibody fragments.

In view of the present claim amendment, which requires that a monovalent antibody fragment prevents the binding of von Willebrand factor (vWF) to human platelet GPIb, any concerns related to antibodies that do not affect the function of GPIb are not applicable to Applicants' claimed invention. Further, Applicants note that the Federal Circuit has long held that it is not necessary for all possible embodiments of a claim to be operative in order for that claim to be enabled. *See Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 U.S.P.Q. 409 (Fed. Cir. 1984). As noted above, the proper test of enablement is whether one reasonably skilled in the art could make and use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation. This basis of the enablement rejection should also be withdrawn.

Finally, the Office asserts:

> In view of applicant's admission of page 14 of the brief dated 6/29/06 that Bergmeir teaches that antibody binding to GPIb resulted in thrombocytopenia, regardless of whether the antibody is a F(ab)2, Fab or

> scFv, therefore, it cannot be seen how any monovalent antibody fragment including Fab or single variable domain can be used in a pharmaceutical composition in vivo since they cause thrombocytopenia.

Applicants note that Bergmeier believed that thrombocytopenia results from the binding between the antibody and its GPIb epitope. Applicants in fact have proved Bergmeier to be incorrect. See, for example, Applicants' specification at page 8 (lines 19-23). Thus, Applicants submit that this line of reasoning does not support the asserted lack of enablement of the presently claimed invention.

For all of the above reasons, Applicants request reconsideration and withdrawal of the enablement rejection.

Rejection under 35 U.S.C. § 102(b)

Claims 65-66 were rejected under 35 U.S.C. § 102(a) as being unpatentable in view of Tandon et al. (Biochem. J. (1991) 274:435-542; "Tandon") and Wicki et al. (Eur. J. Biochem. (1985) 153(1):1-11; "Wicki"). For the following reasons, Applicants respectfully traverse this rejection.

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention. Tandon and Wicki fail to meet this test.

Both Tandon and Wicki fail to teach a "pharmaceutical composition" as claimed because these references fail to teach not only a composition that includes a concentration of an antibody sufficient to bring about a therapeutic effect, but also fail to teach compositions that are pharmaceutical compositions which would be introduced into an appropriate subject. On this point, Applicants respectfully direct the Examiner's attention to the accompanying Declaration of Dr. Désiré Collen (¶¶ 3 - 11).

The Tandon and Wicki antibody compositions are also not pharmaceutical compositions because each lacks the sterility which is required for every pharmaceutical composition; including compositions that include an antibody (Collen, ¶ 7). Moreover because Tandon and Wicki were investigating the role of GP1b in platelet function *in*

vitro, the compositions used by Tandon and Wicki are prepared by methods that do not include a sterilization step (Collen, ¶ 7). Applicants also note that sterilization is an essential step in the preparation of pharmaceutical compositions. Accordingly, implicit in the meaning of the phrase "pharmaceutical composition" is a composition that is not only safe but one that also minimizes the possibility of introducing infection upon introduction into a subject. Tandon and Wicki each fail to disclose such a pharmaceutical composition and therefore cannot anticipate claim 65 or its dependent claims.

The Tandon and Wicki compositions are also not pharmaceutical compositions because the Tandon and Wicki compositions are neither selected in view of tolerance by the patient nor based on the desired activity of the GP1b antibody fragment (Collen, ¶ 8). Indeed, antibody fragments are generally provided in pharmaceutical compositions either freeze-dried or in saline, or in another physiologically neutral solution (Collen, ¶ 8). The inclusion of buffers typically used in *in vitro* experiments renders such compositions unsuitable as pharmaceutical compositions (Collen, ¶ 8).

Applicants further note that Tandon describes the use of a "Buffer A." Buffer A includes 50mM Tris and 0.5%BSA. Tris (or Trishydroxymethylaminomethane) is an irritating product and is generally used for its strong buffering capacity, which can be relevant when working with different reagents in small volumes (Collen, ¶ 9). Tris is not included in a pharmaceutical composition that includes antibody fragments, in view of its toxicity and the fact that antibodies either in the composition or upon administration to the patient remain under physiological conditions, such that there is no need for a strong buffering reagent. BSA (bovine serum albumin) is generally used in in vitro assays to avoid non-specific protein interaction (Collen, ¶ 9). Platelets isolated from their natural environment (blood) are contacted with a BSA-containing buffer to avoid non-specific interaction of any peptide or protein with the platelets (Collen, ¶ 9). There is however no reason to include BSA in a pharmaceutical composition that includes antibody fragments. Indeed, upon administration of the antibodies, the numerous proteins present in the body (including albumin) will ensure that non-specific interactions are avoided (Collen, ¶ 9).

Furthermore, in view of the very strict regulation on the inclusion of bovine products in pharmaceutical compositions, the presence of bovine serum albumin in a composition that includes antibody fragments render such a composition unsuitable as a pharmaceutical composition (Collen, ¶ 9).

Finally, in connection with the Wicki buffer, the Examiner notes that "In order for Fab fragments to be prepared on Ultrogel AcA 34 it must be eluted in a pharmaceutically acceptable carrier." Applicants note that nothing in the Wicki reference teaches that the Ultrogel Aca-34 elution buffer is a pharmaceutical composition. Moreover, no evidence is provided demonstrating that one would understand that an antibody in such an elution buffer would be useful as a pharmaceutical composition. In addition, apart from the sterility issue discussed above, Applicants note that it is common practice to add sodium azide, as an antimicrobial agent, to gel filtration buffers at a concentration around 0.02%. For this reason too, given the toxicity of sodium azide, the Ultrogel AcA-34 elution buffer cannot be considered a pharmaceutical composition.

For all of the above-reasons, the section 102(b) rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed are a Petition to extend the period for replying to the Office Action for three (3) months, to and including March 13, 2007, and authorization for payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 13 March 2007

James D. DeCamp
Reg. No. 43,580

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045